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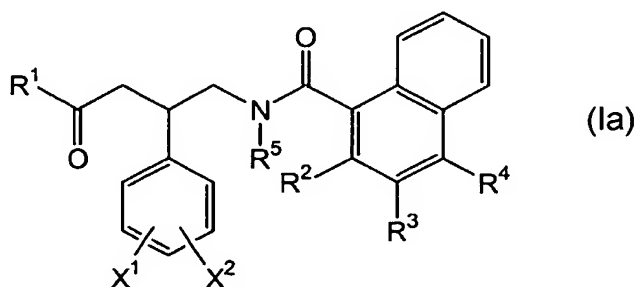
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(54) Title: NAPHTHAMIDE NEUROKININ ANTAGONISTS FOR USE AS MEDICAMENTS



(57) Abstract: A compound having the general formula (Ia) and methods of using such compounds for the treatment of diseases and pharmaceutical composition comprising such compounds.

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COMPOUNDS

Background

The mammalian neurokinins comprise a class of peptide neurotransmitters which are
5 found in the peripheral and central nervous systems. The three principal neurokinins are
Substance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB).

There are also N-terminally extended forms of at least NKA. At least three receptor
types are known for the three principal neurokinins. Based upon their relative selectivities
favoring the neurokinin agonists SP, NKA and NKB, the receptors are classified as
10 neurokinin 1 (NK₁), neurokinin 2 (NK₂) and neurokinin 3 (NK₃) receptors, respectively.

It is now recognized that anxiety, stress, and depression are interrelated conditions
(File SE *Pharmacol, Biochem & Behavior* 54/1:3-12, 1996). Moreover, these complex
emotional states cannot be due simply to defects in a single neurotransmitter although 5-HT
has been ascribed a principal role (Graeff et al., *Pharmacol, Biochem & Behavior* 54/1: 129-
15 141, 1996). Substance P (SP) was one of the first neuropeptides to be identified in
mammalian brain and it is now accepted that all three tachykinins are found within the CNS
(Iversen LL *J Psychopharmacol* 3/1: 1-6, 1989), particularly in the striatonigral neurons,
hypothalamus and limbic forebrain (ibid). NK₁ and NK₃ receptors have been identified in the
brain as well (Beaujouan et al., *Neurosci.* 18: 857-875, 1986). Controversy has existed
20 regarding the presence of the NK₂ receptor in brain, although recent evidence shows receptor
localization in at least the septal region (Steinberg et al., *Eur J Neurosci* 10/7:2337-45 1998).

Pharmacological evidence supporting a role for either NK₁ or NK₂ receptors in anxiety
disorders has been accumulating from assorted animal behavioral tests (for examples, see
Table 1). Animal models of depression, however, have been used rarely to define the
25 potential utility of NK receptor antagonists. SP stimulates the turnover of other
neurotransmitters involved in depression, i.e., 5-HT in the raphe nucleus, an area thought to
be linked to depressive phenomena (Forchetti et al., *J. Neurochem.* 38: 1336-1341, 1982).
When injected centrally to nuclei responsible for control of emotion and stress, SP evokes a
hemodynamic pressor response bridging this peptide to stress induced hypertension (Ku *et al.*,
30 *Peptides*;19/4:677-82, 1998). Moreover, rises in both heart rate and mean arterial blood
pressure evoked by physical stress can be blocked in rodents by centrally administered NK₁
receptor antagonists (Culman et al., *J Pharmacol Exp Ther* 280/1:238-46, 1997).

Table 1. Neurokinin receptor antagonist activity in behavioral tests of anxiety/depression.

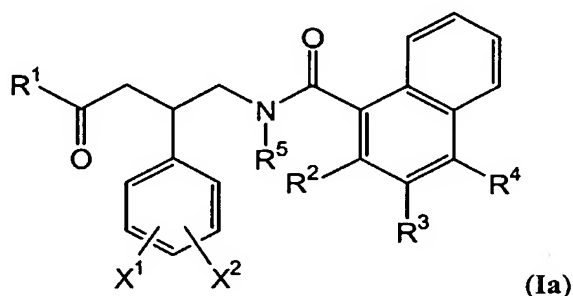
<u>Author</u>	<u>Cpd (Receptor type)</u>	<u>Behavioral Test</u>	<u>Outcome</u>
Teixeira et al., <i>Eur J Pharmacol</i> 5;311(1):7-14, 1996.	NK ₁ agonists & FK888 (NK ₁) SR48968 (NK ₂)	Elevated plus-maze	agonists - anxiogenic antagonists - anxiolytic
File <i>Pharm Bio B</i> 58(3): 747-752, 1997.	CGP 49823 (NK ₁)	Social interaction	anxiolytic
Vassout et al Neuropeptides 26/S1: 38, 1994.	CGP 49823 (NK ₁)	Social interaction test Elevated plus-maze Forced swim test (depression model)	anxiolytic inactive antidepressant (only at 30mg/kg bid)
Stratton et al., <i>Eur. J. Pharmacol.</i> 250: R11-12, 1993.	GR100679 (NK ₂) SR48968 (NK ₂)	Light-dark box	anxiolytic
Walsh et al., <i>Psychopharmacology</i> 121: 186-191, 1995.	GR159897 (NK ₂) SR48968 (NK ₂)	Light-dark box Marmoset human intruder	anxiolytic anxiolytic

Description

This invention relates to butanoic acid naphthamide compounds; to pharmaceutical compositions containing such compounds; as well as to their uses and processes for their preparation. These compounds antagonize the pharmacological actions of the neurokinin 1 (NK₁) receptor. These compounds are useful whenever such antagonism is desired. Thus, such compounds are of value in the treatment of those diseases in which Substance P is implicated, for example, in the treatment of major depressive disorder, severe anxiety disorders, stress disorders, major depressive disorder with anxiety, eating disorders, bipolar disorder, substance use disorder, schizophrenic disorders, psychotic disorders, movement disorders, cognitive disorders, depression and/or anxiety, mania or hypomania, aggressive

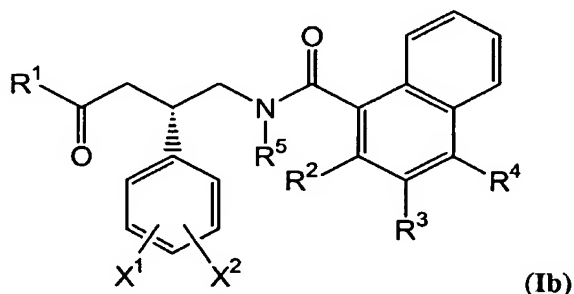
behaviour, obesity, emesis, rheumatoid arthritis, Alzheimer's disease, cancer, oedema, allergic rhinitis, inflammation, pain, gastrointestinal-hypermotility, Huntington's disease, chronic obstructive pulmonary disorder (COPD), hypertension, migraine, bladder hypermotility, or urticaria.

5 Accordingly, the present invention provides the compounds of the general formula Ia:



The compounds of the present invention may possess a number of chiral centres, for example at -CH(Ph-X¹,X²)-. The present invention covers all isomers, diastereoisomers and mixtures thereof that antagonize NK₁.

The preferred configuration at -CH(Ph-X¹,X²)- is shown in formula (Ib) hereinbelow:



X¹ and X² are independently hydrogen, methyl or halogen. Preferably, X¹ and X² are independently hydrogen or halogen provided that at least one of X¹ or X² is halogen. Most favourably, X¹ and X² are both chloro. In a preferred aspect Ph-X¹,X² is 3,4-dichlorophenyl.

R¹ is -OR⁶, -NR⁶R⁷, -NOC₁₋₆alkyl or -NR⁷NR⁶R⁷. In one embodiment, R¹ is -OR⁶ or -NR⁶R⁷. In another embodiment, R¹ is -OR⁶. In another embodiment R¹ is -NR⁶R⁷.

R² is -OR⁶ or C₁₋₄alkyl. Preferably, R² is -CH₂CH₃ or -OCH₃.

R³ is H, halogen, -OR⁷ or -CN. Preferably, R³ is -CN.

R⁴ is H, C₁₋₆alkyl or -OR⁷.

R⁵ is H or C₁₋₆alkyl. Preferably, R⁵ is H or CH₃.

R^6 is independently, at each instance, H, C_{1-6} alkyl, $R^7OC_{1-6}alkyl$ -, $R^7OC(=O)C_{1-6}alkyl$ -, $R^7R^7NC(=O)C_{1-6}alkyl$ -, $R^7R^7NC_{1-6}alkylNR^7C(=O)$ -, R^8 -, $R^8C_{1-6}alkyl$ - or $-(CH_2)_mphenyl$, wherein the phenyl is substituted by 1, 2 or three substituents selected from $C_{1-6}alkylthio$, $C_{1-6}alkylsulfinyl$, $C_{1-6}alkylsulfonyl$, trifluoromethylthio, trifluoromethylsulfinyl,

- 5 $C_{1-6}alkanesulfonamido$, $C_{1-6}alkanoyl$, $C_{1-6}alkoxy-carbonyl$, succinamido, carbamoyl, $C_{1-6}alkylcarbamoyl$, di- $C_{1-6}alkylcarbamoyl$, $C_{1-6}alkoxy-C_{1-6}alkylcarbamoyl$, N-methylcarbamoyl, $C_{1-6}alkanoylamino$, ureido, $C_{1-6}ureido$, di- $C_{1-6}alkylureido$, amino, $C_{1-6}alkylamino$ and di- $C_{1-6}alkylamino$. In another embodiment, R^6 is independently, at each instance, H, $C_{1-6}alkyl$, or $-(CH_2)_mphenyl$, wherein the phenyl is substituted by 1, 2 or three
- 10 substituents selected from $C_{1-6}alkylthio$, $C_{1-6}alkylsulfinyl$, $C_{1-6}alkylsulfonyl$, trifluoromethylthio, trifluoromethylsulfinyl, $C_{1-6}alkanesulfonamido$, $C_{1-6}alkanoyl$, $C_{1-6}alkoxy-carbonyl$, succinamido, carbamoyl, $C_{1-6}alkylcarbamoyl$, di- $C_{1-6}alkylcarbamoyl$, $C_{1-6}alkoxy-C_{1-6}alkylcarbamoyl$, N-methylcarbamoyl, $C_{1-6}alkanoylamino$, ureido, $C_{1-6}ureido$, di- $C_{1-6}alkylureido$, amino, $C_{1-6}alkylamino$ and di- $C_{1-6}alkylamino$.

- 15 R^7 is H or $C_{1-6}alkyl$.

In one embodiment, R^6 and R^7 together are $-(CH_2)_2O(CH_2)_2$ -, $-(CH_2)_2S(=O)_m(CH_2)_2$ -, $-(CH_2)_2N(CO_2R^7)(CH_2)_2$ - or $-(CH_2)_2NR^7(CH_2)_2$ -.

R^8 is a 5- or 6-membered saturated or unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms and additionally substituted with 0 or 1 oxo groups.

- 20 m is 0, 1 or 2.

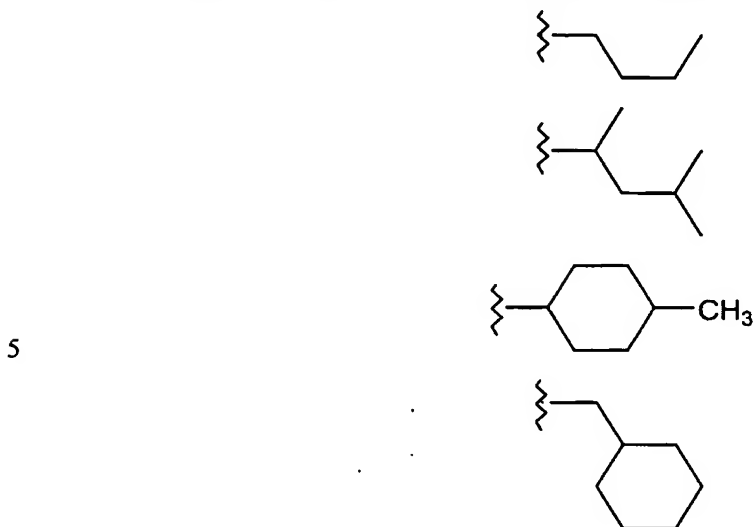
Another aspect of the invention involves a pharmaceutical composition comprising a compound of formula Ia.

- Another aspect of the invention involves a method of treating major depressive disorder, severe anxiety disorders, stress disorders, major depressive disorder with anxiety,
- 25 eating disorders, bipolar disorder, substance use disorder, schizophrenic disorders, psychotic disorders, movement disorders, cognitive disorders, depression and/or anxiety, mania or hypomania, aggressive behaviour, obesity, emesis, rheumatoid arthritis, Alzheimer's disease, cancer, oedema, allergic rhinitis, inflammation, pain, gastrointestinal-hypermotility, Huntington's disease, COPD, hypertension, migraine, bladder hypermotility, or urticaria
- 30 comprising administering an effective amount of an NK_1 antagonist of formula Ia.

Particular compounds of this invention are provided as the Examples hereinbelow.

$C_{Y-Z}alkyl$, unless otherwise specified, means an alkyl chain containing a minimum Y total carbon atoms and a maximum Z total carbon atoms. These alkyl chains may be

branched or unbranched, cyclic, acyclic or a combination of cyclic and acyclic. For example, the following substituents would be included in the general description "C₄₋₇alkyl":



Pharmaceutically-acceptable salts may be prepared from the corresponding acid in conventional manner. Non-pharmaceutically-acceptable salts may be useful as intermediates and as such are another aspect of the present invention.

10 The term "oxo" means a double bonded oxygen (=O).

Some of the compounds of the present invention are capable of forming salts with various inorganic and organic acids and bases and such salts are also within the scope of this invention. Examples of such acid addition salts include acetate, adipate, ascorbate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, cyclohexyl
 15 sulfamate, ethanesulfonate, fumarate, glutamate, glycolate, hemisulfate, 2-hydroxyethyl-sulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, hydroxymaleate, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, nitrate, oxalate, pamoate, persulfate, phenylacetate, phosphate, picrate, pivalate, propionate, quinate, salicylate, stearate, succinate, sulfamate, sulfanilate, sulfate, tartrate, tosylate (p-
 20 toluenesulfonate), and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as aluminum, calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, ornithine, and so forth. Also, basic nitrogen-containing groups may be quaternized with such agents as: lower
 25 alkyl halides, such as methyl, ethyl, propyl, and butyl halides; dialkyl sulfates like dimethyl, diethyl, dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl

halides; aralkyl halides like benzyl bromide and others. Non-toxic physiologically-acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base
5 form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water, which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion-exchange resin.

In order to use a compound of the formula (I) or a pharmaceutically acceptable salt
10 thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable
15 salt and pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation or insufflation. For these purposes the compounds of this invention may be formulated by means known in the art
20 into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols or nebulisers for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition
25 of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to herein.

The pharmaceutical compositions of this invention will normally be administered to
30 humans so that, for example, a daily dose of 0.01 to 25 mg/kg body weight (and preferably of 0.1 to 5 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration

depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention. For example a tablet or capsule for oral administration may conveniently contain
5 up to 250 mg (and typically 5 to 100 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof. In another example, for administration by inhalation, a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be administered in a daily dosage range of 5 to 100 mg, in a single dose or divided into two to four daily doses. In a further example, for administration by intravenous or intramuscular
10 injection or infusion, a sterile solution or suspension containing up to 10% w/w (and typically 5% w/w) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof may be used.

Therefore in a further aspect, the present invention provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof for use in a method of therapeutic
15 treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein antagonism of the NK₁ receptor is beneficial which comprises administering to a warm-blooded animal an effective amount of a compound of the formula (I) or a pharmaceutically-acceptable salt thereof. The present invention also provides the use
20 of a compound of the formula (I) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for use in a disease condition wherein antagonism of the NK₁ receptor is beneficial.

The compounds of the formula (I) and their pharmaceutically acceptable salts may be made by processes as described and exemplified herein and by processes similar thereto and
25 by processes known in the chemical art. If not commercially available, starting materials for these processes may be made by procedures which are selected from the chemical art using techniques which are similar or analogous to the synthesis of known compounds.

It is well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form or by synthesis from optically-active starting materials) and
30 how to determine the NK₁ antagonist properties by the standard tests known in the art and those described hereinafter.

Some individual compounds within the scope of this invention may contain double bonds. Representations of double bonds in this invention are meant to include both the E and

the Z isomer of the double bond. Additionally, some species within the scope of this invention may contain one or more asymmetric centers. This invention includes the use of any of the optically pure stereoisomers as well as any combination of stereoisomers.

Some compounds bearing a 2-substituted naphthamide can exist as a mixture of conformational isomers (atropisomers) ("The Chemistry of Rotational Isomers"; Oki, M.; Springer Verlag, NY; 1993). Where individual atropisomers have been isolatable, distinct chemical and biological properties have been observed. The compounds of this invention comprise both mixtures of, and individual, atropisomers.

The following biological test methods, data and Examples serve to illustrate and further describe the invention.

The utility of a compound of the invention or a pharmaceutically acceptable salt thereof (hereinafter, collectively referred to as a "compound") may be demonstrated by standard tests and clinical studies, including those disclosed in the publications described below.

SP Receptor Binding Assay (Test A)

The ability of a compound of the invention to antagonize the binding of SP at the NK₁ receptor may be demonstrated using an assay using the human NK₁ receptor expressed in Mouse Erythroleukemia (MEL) cells. The human NK₁ receptor was isolated and characterized as described in: B. Hopkins, et al. "Isolation and characterization of the human lung NK₁ receptor cDNA" Biochem. Biophys. Res. Comm., 1991, **180**, 1110-1117; and the NK₁ receptor was expressed in Mouse Erythroleukemia (MEL) cells using a procedure similar to that described in Test B below.

Neurokinin A (NKA) Receptor Binding Assay (Test B)

The ability of a compound of the invention to antagonize the binding of NKA at the NK₂ receptor may be demonstrated using an assay using the human NK₂ receptor expressed in Mouse Erythroleukemia (MEL) cells, as described in: Aharony, D., et al. "Isolation and Pharmacological Characterization of a Hampster Neurokinin A Receptor cDNA" Molecular Pharmacology, 1994, **45**, 9-19.

The selectivity of a compound for binding at the NK₁ and the NK₂ receptors may be shown by determining its binding at other receptors using standard assays, for example, one using a tritiated derivative of NKB in a tissue preparation selective for NK₃ receptors. In general, the compounds of the invention which were tested demonstrated statistically

significant binding activity in Test A and Test B with a K_i of 1 mM or much less typically being measured.

Rabbit Pulmonary Artery: NK_1 in vitro functional assay (Test C)

The ability of a compound of the invention to antagonize the action of the agonist Ac-
5 [Arg⁶, Sar⁹, Met(O₂)¹¹] Substance P (6-11), ASMSP, in a pulmonary tissue may be demonstrated as follows.

Male New Zealand white rabbits are euthanized via i.v. injection into the ear vein with
60 mg/kg Nembutal (50 mg/mL). Preceding the Nembutal into the vein is Heparin (1000
units/mL) at 0.0025 mL/kg for anticoagulant purposes. The chest cavity is opened from the
10 top of the rib cage to the sternum and the heart, lungs and part of the trachea are removed.
The pulmonary arteries are isolated from the rest of the tissues and cut in half to serve as
pairs.

The segments are suspended between stainless steel stirrups, so as not to remove any
of the endothelium, and placed in water-jacketed (37.0 °C) tissue baths containing
15 physiological salt solution of the following composition (mM): NaCl, 118.0; KCl, 4.7; CaCl₂,
1.8; MgCl₂, 0.54; NaH₂PO₄, 1.0; NaHCO₃, 25.0; glucose, 11.0; indomethacin, 0.005 (to
inhibit cyclooxygenase); and *dl*-Propranolol, 0.001 (to block β receptors); gassed continuously
with 95% O₂-5% CO₂. Responses are measured on a Grass polygraph via Grass FT-03
transducers.

20 Initial tension placed on each tissue is 2 grams, which is maintained throughout the
1.0 hour equilibration period. Tissues are washed with the physiological salt solution at 15
minute intervals. At the 30 and 45 minute wash the following treatments are added: 1×10^{-6}
M Thiorphan (to block E.C.3.4.24.11), 3×10^{-8} M (S)-N-[2-(3,4-dichlorophenyl)-4-[4-(2-
oxoperhydropyrimidin-1-yl)piperidino]butyl]-N-methylbenzamide (to block NK_2 receptors),
25 and the given concentration of the compound being tested. At the end of the 1.0 h
equilibration, 3×10^{-6} M Phenylephrine hydrochloride is added for 1.0 h. At the end of 1.0 h,
a dose relaxation curve to ASMSP is done. Each tissue is treated as a individual and is
considered finished when it fails to relax further for 2 consecutive doses. When a tissue is
complete, 1×10^{-3} M Papaverine is added for maximum relaxation.

30 Percent inhibition is determined when a tested compound produces a statistically
significant ($p < 0.05$) reduction of the total relaxation which is calculated using the total
relaxation of the Papaverine as 100%. Potencies of the compounds are determined by

calculating the apparent dissociation constants (K_B) for each concentration tested using the standard equation:

$$KB = [\text{antagonist}] / (\text{dose ratio} - 1)$$

where dose ratio = $\text{antilog}[(\text{agonist } -\log \text{ molar } EC_{50} \text{ without compound}) - (-\log \text{ molar } EC_{50} \text{ with compound})]$. The K_B values may be converted to the negative logarithms and expressed as $-\log \text{ molar } KB$ (i.e. pK_B). For this evaluation, complete concentration-response curves for agonist obtained in the absence and presence of the compound tested using paired pulmonary artery rings. The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The EC_{50} values are converted to negative logarithms and expressed as $-\log$ molar EC_{50} .

NK₂ in vitro functional assay (Test D)

The ability of a compound of the invention to antagonize the action of the agonist [β -ala8] NKA (4-10), BANK, in a pulmonary tissue may be demonstrated as follows. Male New Zealand white rabbits are euthanized via i.v. injection into the ear vein with 60 mg/kg Nembutal (50 mg/mL). Preceding the Nembutal into the vein is Heparin (1000 units/mL) at 0.0025 mL/kg for anticoagulant purposes. The chest cavity is opened from the top of the rib cage to the sternum and a small incision is made into the heart so that the left and right pulmonary arteries can be cannulated with polyethylene tubing (PE260 and PE190 respectively). The pulmonary arteries are isolated from the rest of the tissues, then rubbed over an intimal surface to remove the endothelium, and cut in half to serve as pairs. The segments are suspended between stainless steel stirrups and placed in water-jacketed (37.0 °C) tissue baths containing physiological salt solution of the following composition (mM): NaCl, 118.0; KCl, 4.7; CaCl₂, 1.8; MgCl₂, 0.54; NaH₂PO₄, 1.0; NaHCO₃, 25.0; glucose, 11.0; and indomethacin, 0.005 (to inhibit cyclooxygenase); gassed continuously with 95% O₂-5% CO₂. Responses are measured on a Grass polygraph via Grass FT-03 transducers.

Initial tension placed on each tissue is 2 g, which is maintained throughout the 45 min equilibration period. Tissues are washed with the physiological salt solution at 15 min intervals. After the 45 min equilibration period, 3×10^{-2} M KCl is given for 60 min to test the viability of the tissues. The tissues are then washed extensively for 30 min. The concentration of the compound being tested is then added for 30 min. At the end of the 30 min, a cumulative dose response curve to BANK is performed. Each tissue is treated as a individual and is considered finished when it fails to contract further for 2 consecutive doses. When a tissue is complete, 3×10^{-2} M BaCl₂ is added for maximum contraction.

Percent inhibition is determined when a tested compound produces a statistically significant ($p < 0.05$) reduction of the total contraction which is calculated using the total contraction of the BaCl_2 as 100%. Potencies of the compounds are determined by calculating the apparent dissociation constants (K_B) for each concentration tested using the standard equation:

$$K_B = [\text{antagonist}] / (\text{dose ratio} - 1)$$

where dose ratio = $\text{antilog}[(\text{agonist} - \log \text{molar } EC_{50} \text{ without compound}) - (\log \text{molar } EC_{50} \text{ with compound})]$. The K_B values may be converted to the negative logarithms and expressed as $-\log \text{molar } K_B$ (i.e. pK_B). For this evaluation, complete concentration-response curves for agonist obtained in the absence and presence of the compound tested using paired pulmonary artery rings. The potency of the agonist is determined at 50% of its own maximum relaxation in each curve. The EC_{50} values are converted to negative logarithms and expressed as $-\log \text{molar } EC_{50}$.

NK₁ and NK₂ in vivo functional assay (Test E)

The activity of a compound as an antagonist of NK₁ and/or NK₂ receptors also may be demonstrated in vivo in laboratory animals as described in: Buckner et al. "Differential Blockade by Tachykinin NK₁ and NK₂ Receptor Antagonists of Bronchoconstriction Induced by Direct-Acting Agonists and the Indirect-Acting Mimetics Capsaicin, Serotonin and 2-Methyl-Serotonin in the Anesthetized Guinea Pig." *J. Pharm. Exp. Ther.*, 1993, Vol 267(3), pp.1168-1175. The assay is carried out as follows.

Compounds are tested in anesthetized guinea pigs pretreated with i.v. indomethacin (10 mg/kg, 20 min), propranolol (0.5 mg/kg, 15 min), and thiorphan (10 mg/kg, 10 min).

Antagonists or vehicle are administered i.v. and orally, 30 and 120 min prior to increasing concentrations of agonist, respectively. The agonists used in these studies are ASMSP (Ac-[Arg⁶,Sar⁹,Met(O₂)¹¹]-SP(6-11)) and BANK (β-ala-8 NKA4-10).

Administered i.v., ASMSP is selective for NK₁ receptors, and BANK is selective for NK₂ receptors. Maximum response is defined as zero conductance (G_t , 1/Rp). ED_{50} values are calculated (the dose of agonist resulting in a reduction of G_t to 50% of baseline), and converted to the negative logarithm ($-\log ED_{50}$). The ED_{50} values, obtained in the presence (P) and absence (A) of antagonist, are used to calculate a Dose Ratio (P/A), an expression of potency. Data are expressed as mean \pm SEM and statistical differences were determined using ANOVA/Tukey-Kramer and Student's t-test, with $p < 0.05$ considered statistically significant.

Compounds of the present invention exhibit marked activity in the foregoing tests and are considered useful for the treatment of those diseases in which the NK₁ and/or NK₂ receptor is implicated, for example, in the treatment of asthma and related conditions.

5 **Examples**

The invention will now be illustrated by the following non-limiting examples, in which, unless stated otherwise:

- (i) temperatures are given in degrees Celsius (°C); unless otherwise stated, operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25 °C;
- (ii) organic solutions were dried over anhydrous magnesium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60 °C;
- (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
- (iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;
- (v) melting points are uncorrected and (dec) indicates decomposition;
- (vi) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using deuterated chloroform (CDCl₃) as solvent; conventional abbreviations for signal shape are used; for AB spectra the directly observed shifts are reported; coupling constants (J) are given in Hz; Ar designates an aromatic proton when such an assignment is made;
- (viii) reduced pressures are given as absolute pressures in pascals (Pa); elevated pressures are given as gauge pressures in bars;
- (ix) solvent ratios are given in volume:volume (v/v) terms; and
- (x) Mass spectra (MS) were run using an automated system with atmospheric pressure chemical ionization (APCI). Generally, only spectra where parent masses are observed are reported. The lowest mass major ion is reported for molecules where isotope splitting results in multiple mass spectral peaks (for example when chlorine is present).

Terms and abbreviations: solvent mixture compositions are given as volume percentages or volume ratios. In cases where the NMR spectra are complex, only diagnostic signals are reported. atm = atmospheric pressure, Boc = t-butoxycarbonyl, Cbz = benzyloxy-carbonyl, DCM = methylene chloride, DIPEA = diisopropylethylamine, DMF = N,N-
5 dimethylformamide, DMSO = dimethyl sulfoxide, Et₂O = diethyl ether, EtOAc = ethyl acetate, equiv. = equivalent(s), h = hour(s), HPLC = high performance liquid chroma-
tography, min = minutes, NMR = nuclear magnetic resonance, psi = pounds per square inch, TFA = trifluoroacetic acid, THF = tetrahydrofuran.

Standard reductive amination refers to the typical procedure in which a solution of an
10 amine (1-1.2 equiv.), an aldehyde (1-1.2 equiv.) and acetic acid (2 equiv.) is stirred in methanol for 5 to 60 min before adding NaBH₃CN (1.7 equiv.). After 1-16 h the reaction is optionally concentrated, dissolved in DCM, and washed with saturated sodium bicarbonate and then purified by chromatography.

Standard Swern oxidation conditions refer to the oxidation of an alcohol to the
15 corresponding aldehyde according to Mancuso, AJ; Huang, SL; Swern, D; J. Org. Chem.; 1978, 2840.

Standard formation of an acid chloride refers to the typical procedure in which a solution of a substituted carboxylic acid in DCM is stirred with 1-1.2 equiv. of oxalyl chloride and a catalytic amount of DMF for 1-12 h, concentrated under reduced pressure, and used
20 without purification.

Standard acylation refers to the typical procedure in which an acid chloride (1-1.2 equiv.) is added to a stirred solution of an amine (1-1.2 equiv.) and triethylamine (2 equiv.) in DCM. After 1-16 h the reaction is optionally concentrated, dissolved in DCM, and washed with saturated sodium bicarbonate and then purified by chromatography.

25 Where noted that a final compound was converted to the citrate salt, the free base was combined with citric acid (1.0 equiv.) in methanol, concentrated under reduced pressure and dried under vacuum (25-70 °C). When indicated that a compound was isolated by filtration from Et₂O, the citrate salt of the compound was stirred in Et₂O for 12-18 h, removed by filtration, washed with Et₂O, and dried under vacuum at 25-70 °C.

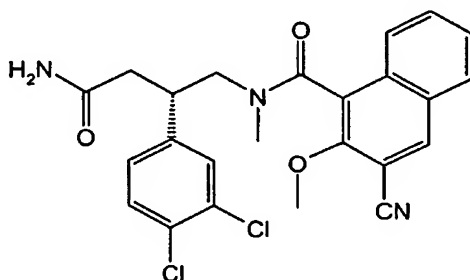
30 Where noted that a final compound was converted to the hydrochloride salt, a solution of HCl in Et₂O was added with stirring to a solution of the purified free base in DCM or methanol. The resulting precipitate was collected by filtration and dried under vacuum.

Analytical HPLC conditions employed were the following: Hewlett Packard HP1100 system using a Luna C18(2) 4.6x75 mm, 3 micron column (Phenomenex; Torrance, CA) with the following gradient: 0-0.5 min; 20% Solvent B, then ramping linearly to 85% Solvent B at 15 min at a fixed flow rate of 2 mL/min (Solvent A: 0.1% TFA in water; Solvent B: 0.1%

5 TFA in methanol) using UV detection at 255 nm.

Example 1

N-[2-(S)-(3,4-Dichlorophenyl)-3-aminocarbonylpropyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide



10 To a stirred solution of N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide and diisopropylethyl amine (2.0 equiv.) in DCM was added tetramethyl fluoroformamidinium hexafluorophosphate (TFFH) (1.2 equiv.). After 20 min, ammonium hydroxybenzotriazole (1.2 equiv., Bajusz, S; et al.; Fed. Eur. Biochem. Soc.; 1977, 76, 91) was added. After 30 min, the solution was extracted with saturated sodium
15 bicarbonate, 1M HCl, and water, then purified by flash chromatography (80%). ¹H NMR (300 MHz, DMSO-d₆) δ 8.64-8.62 (m), 8.08-7.94 (m), 7.78-7.72 (m), 7.70 (s), 7.67 (s), 7.63-7.58 (m), 7.56-7.50 (m), 7.46-7.39 (m), 7.36-7.32 (m), 7.11 (bs); 7.01-6.98 (m), 6.85-6.76 (m), 6.37-6.34 (d), 4.51-4.43 (t), 4.08-3.99 (m), 3.94 (s), 3.91 (s), 3.73-3.71 (m), 3.67 (s), 3.64-3.61 (m), 3.46-3.28 (m), 3.13 (s), 3.11 (s), 3.06 (s), 2.69 (s), 2.62 (s), 2.56-2.44 (m),
20 2.34-2.27 (m), 2.16-2.11 (m), 2.07 (s); MS APCI, m/z = 470 (M⁺); HPLC 11.82.

The requisite N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide was prepared as follows.

(a) 3-Hydroxy-4-iodo-2-naphthoic acid.

A mixture of NaOH (2.12 g) in methanol (100 mL) was stirred until the solution was
25 homogeneous. Sodium iodide (3.98 g) and 3-hydroxy-2-naphthoic acid (5.00 g) were added and allowed to stir for 30 min. The resulting suspension was cooled to 0 °C and a 5.25% (w/v) aqueous solution of sodium hypochlorite was added dropwise and stirring continued for 1 h. Saturated sodium thiosulfate (25 mL) was added and after 5 min the solution was

acidified to pH 2 by addition of 6 N HCl resulting in the formation of a yellow precipitate which was filtered and washed with water (50 mL). The precipitate was transferred to a round-bottomed flask, dissolved in methanol (70 mL) and toluene (100 mL), concentrated, redissolved in methanol (70 mL), concentrated, redissolved again in methanol (70 mL) and toluene (100 mL) and concentrated to afford the product as a yellow solid (6.26 g). MS m/z 313 (M-1). ¹H NMR (DMSO-*d*₆): δ 12.41 (broad, 1 H), 8.63 (s, 1 H), 8.05-7.97 (m, 2 H), 7.70 (m, 1 H), 7.42 (m, 1H).

(b) Methyl 3-methoxy-4-iodo-2-naphthoate

A solution of 3-hydroxy-4-iodo-2-naphthoic acid (8.0 g), dimethyl sulfate (8.03 g), powdered potassium carbonate (8.80 g), and dry acetone (150 mL) was heated under reflux for 18 h. The solution was cooled to room temperature, triethylamine (15 mL) was added, and stirring continued for 30 min. The solution was filtered through a pad of Celite and washed with dry acetone (50 mL). The filtrate was concentrated to a yellow oil, diluted with EtOAc, and washed successively with 1N HCl (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL). The organic phase was dried (sodium sulfate), filtered, concentrated, and purified by chromatography (0-10% EtOAc in hexanes) to afford the product as a yellow oil (5.53 g). ¹H NMR (DMSO-*d*₆) δ 8.47 (s, 1 H), 8.09 (m, 2 H), 7.74 (m, 1 H), 7.61 (m, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H).

(c) 1-Iodo-3-cyano-2-methoxynaphthalene

Based on the procedure of Wood, JL; Khatri, NA; Weinreb, SM; Tetrahedron Lett; 51, 4907 (1979), methyl 3-methoxy-4-iodo-2-naphthoate (5.0 g) was suspended in xylenes (100 mL), cooled to 0 °C, dimethylaluminum amide solution (approximately 37 mmol) was added and the solution heated under reflux for 2.5 h. The solution was then cooled to 0 °C and the solution was acidified to pH 2 by addition of 1N HCl and extracted with EtOAc (3x100 mL). The combined EtOAc extracts were washed with saturated aqueous sodium bicarbonate (150 mL) and brine (150 mL), dried (sodium sulfate), filtered, concentrated, and purified by chromatography (1:1 EtOAc:DCM, then 10-20% EtOAc in DCM) to afford the product as a white solid (3.29 g). ¹H NMR (DMSO-*d*₆): δ 8.69 (s, 1 H), 8.24-8.04 (m, 2 H), 7.91-7.81 (m, 1 H), 7.76-7.65 (m, 1 H), 3.99 (s, 3 H); MS m/z 311 (M+H).

(d) Methyl 3-cyano-2-methoxy-1-naphthoate

Through a suspension of 1-iodo-3-cyano-2-methoxynaphthalene (0.250 g), Pd(OAc)₂ (0.018 g), triethylamine (0.081 g) and methanol (20 mL) was bubbled carbon monoxide for 25 min, then stirred at 70 °C under carbon monoxide (1 atm) for 18 h. The cooled solution

was filtered, rinsed with methanol (20 mL) and DCM (20 mL), concentrated, preadsorbed onto silica (1 g) and purified by chromatography (0-10% EtOAc in hexanes) to afford the product as a white solid (0.113g). ¹H NMR (DMSO-d₆): δ 8.78 (s, 1 H), 8.12-8.09 (m, 1 H), 7.84-7.78 (m, 2 H), 7.70-7.63 (m, 1 H), 4.02-4.01 (m, 6 H); IR (cm⁻¹): 2228, 1724, 1296, 1236, 1208, 1017.

(e) 3-Cyano-2-methoxy-1-naphthoic acid

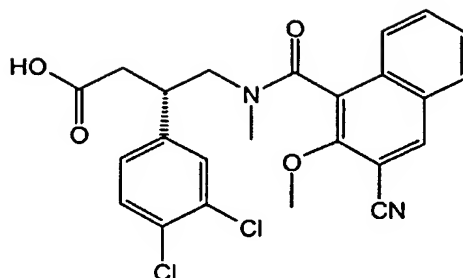
A solution of methyl 3-cyano-2-methoxy-1-naphthoate (0.113 g) and LiOH•H₂O (0.0196 g) THF (3 mL), water (1 mL) and methanol (1 mL) was stirred overnight at room temperature. The solution was diluted with saturated sodium bicarbonate and extracted with Et₂O. The aqueous layer was acidified to pH 2 by addition of 1N HCl and extracted with Et₂O. The organic layer was washed with water (30 mL) and brine (40 mL), dried (sodium sulfate), filtered, and concentrated to a white solid. ¹H NMR (DMSO-d₆): δ 14.06 (broad, 1 H), 8.08-8.02 (m, 1 H), 7.83-7.76 (m, 2 H), 7.69-7.63 (m, 1 H), 4.02 (s, 3 H); MS m/z: 226 (M-1).

(f) N-[2-(S)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide

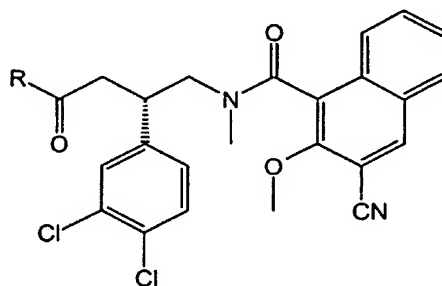
A solution of N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-N-methylamine (Miller, SC; WO 9512577) in DCM was combined with 10% aqueous sodium bicarbonate solution. The mixture was cooled to 0 °C and a solution of 3-cyano-2-methoxy-1-naphthoyl chloride (prepared from 3-cyano-2-methoxy-1-naphthoic acid using oxalyl chloride) in DCM was added dropwise over 30 min. After stirring overnight at room temperature, the organic phase was concentrated and purified by column chromatography to afford N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide. ¹H NMR (300 MHz, DMSO-d₆) δ 8.67-8.58 (m), 8.07-8.00 (m), 7.72-7.65 (m), 7.64-7.43 (m), 7.42-7.34 (m), 7.02-7.01 (m), 6.98-6.87 (d), 6.77-6.74 (d), 6.31-6.28 (d), 4.55-4.52 (t), 4.35-4.34 (t), 4.03-3.92 (m), 3.78-3.72 (m), 3.68 (s), 3.45-3.37 (m), 3.29-2.89 (m), 2.73 (s), 2.59-2.49 (m), 1.91-1.78 (m), 1.58-1.46 (m); MS APCI, m/z = 457 (M+).

(g) N-[2-(S)-(3,4-Dichlorophenyl)-3-carboxypropyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide

- 17 -



According to the procedure of Corey, EJ and Schmidt, G, Tetr. Lett., 1979, 399, a solution of pyridinium dichromate (4.5 g) was added to a solution of N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide (1.5 g) in DMF (20 mL) and stirred for 4 h. After filtration, dilution with ethyl acetate, and aqueous extraction of the filtrate, the product was purified by flash chromatography (80%). ¹H NMR (300 MHz, DMSO-d₆) δ 12.28 (s), 8.66-8.62 (m), 8.09-7.95 (m), 7.78-7.76 (m), 7.72-7.56 (m), 7.52-7.45 (m), 7.40-7.30 (m), 7.11-7.10 (d), 7.04 (s), 7.01 (s), 6.87-6.84 (d), 4.53-4.45 (t), 3.94 (s), 3.92 (s), 3.68 (s), 3.44-3.27 (m), 3.11 (s), 3.02 (s), 2.76-2.73 (m), 2.62 (s), 2.55-2.38 (m); MS APCI, m/z = 471 (M⁺).



Ex.	R	MS ^a	HPLC ^b	Synthesis
2	-OH	472	11.81, 12.12, 12.55	See Example 1 step (g)
3	-N(CH ₃) ₂	498	11.78, 12.32, 12.76	Dimethylamine ^d (solution in THF; 4 equiv.)
4	-NHC(CH ₃) ₃	526	12.95, 13.39, 13.99, 14.15	tert-Butylamine ^d (4 equiv.)
5	-NHCH ₃	484	10.88, 11.39, 12.15, 12.26	Methylamine ^d (solution in THF; 4 equiv.)

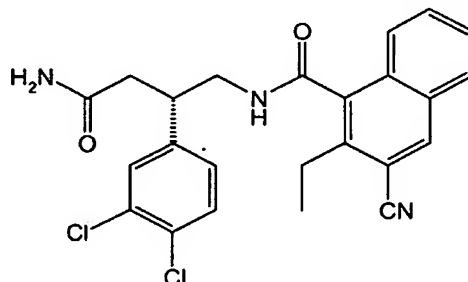
Ex.	R	MS ^a	HPLC ^b	Synthesis
6	-OCH ₃	486	13.10 13.48	Methyl iodide ^c

^aMass spectral data; (APCI) m/z. Multiple peaks due to isotopic splitting are not considered; data for the major isotopically abundant signal corresponding to the protonated molecular ion cluster are shown (unless noted otherwise). ^b See general experimental section for HPLC

5 conditions, retention times in minutes; "nd" indicates not determined. ^d The indicated amine was reacted with N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-N-methyl-3-cyano-2-methoxy-1-naphthoyl chloride (prepared from N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-N-methyl-3-cyano-2-methoxy-1-naphthamide using the standard defined conditions for acid chloride formation) using the standard defined conditions for acylation. ^e Prepared by
 10 reaction of the material of Example 2 with K₂CO₃ (2 equiv.) and methyl iodide (1.2 equiv.) in DMF for 2 h.

Example 7

N-[2-(S)-(3,4-Dichlorophenyl)-3-aminocarbonylpropyl]-3-cyano-2-ethyl-1-naphthamide



15 To a stirred solution of N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-3-cyano-2-ethyl-1-naphthamide and ammonium hydroxybenzotriazole (2.6 equiv.) in DMF was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.2 equiv). After 18 h, the solution was poured into saturated aqueous sodium bicarbonate and extracted with DCM. The DCM extracts were concentrated, and the residue was purified by flash chromatography
 20 (73%). ¹H NMR (300 MHz, DMSO-d₆) δ 8.74-8.63 (m), 8.58 (s), 8.07-7.92 (m), 7.71-7.46 (m), 7.45-7.22 (m), 6.87-6.85 (d), 6.79 (s), 4.01-3.77 (m), 3.61-3.20 (m), 2.82-2.63 (m), 2.59-2.23 (m), 1.21-1.16 (t), 1.02-0.97 (t); MS APCI, m/z = 454.1 (M⁺); HPLC 17.5 min.

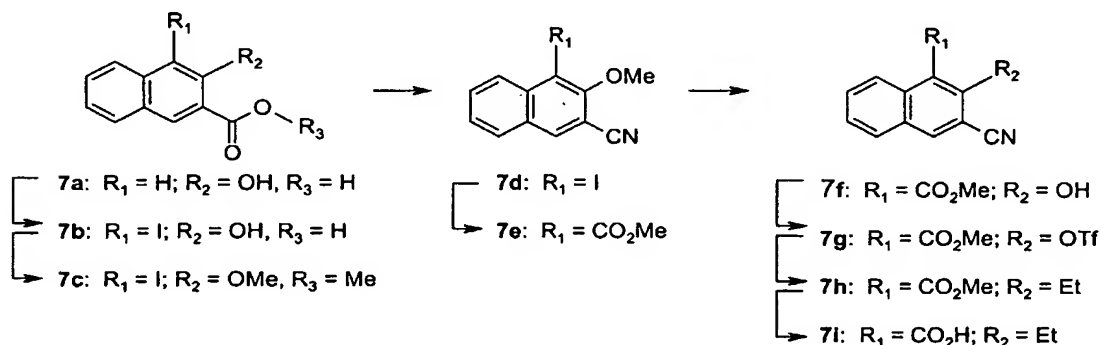
Analytical HPLC conditions employed were the following: Hewlett Packard HP1050 system using a Zorbax RX-C8, 4.6x250 mm, 5 micron column at 30 °C, with the following gradient:
 25 0-0.5 min; 10% Solvent B, then ramping linearly to 100% Solvent B at 30 min at a fixed flow

rate of 1.2 mL/min (Solvent A: 0.1% TFA in water; Solvent B: 0.1% TFA in acetonitrile); UV detection at 215 nm.

N-[2-(S)-(3,4-Dichlorophenyl)-3-carboxypropyl]-3-cyano-2-ethyl-1-naphthamide was prepared as follows:

- 5 N-[2-(S)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-3-cyano-2-ethyl-1-naphthamide was prepared according to methods described for Example 1, step (f) using N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-amine (Miller, SC; WO 9410146) in place of N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-N-methylamine and using 3-cyano-2-ethyl-1-naphthoyl chloride in place of 3-cyano-2-methoxy-1-naphthoyl chloride. N-[2-(S)-(3,4-
- 10 Dichlorophenyl)-3-carboxypropyl]-3-cyano-2-ethyl-1-naphthamide was prepared by Jones oxidation (Fieser, LF, Fieser, M; "Reagents for Organic Synthesis", Vol. 1, Wiley, 1967, p. 142) of N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-3-cyano-2-ethyl-1-naphthamide. 3-Cyano-2-ethyl-1-naphthoyl chloride was prepared from 3-cyano-2-ethyl-1-naphthoic acid (7i) using oxalyl chloride. 3-Cyano-2-ethyl-1-naphthoic acid (7i) was prepared as follows.

15



7b

- A mixture of NaOH (2.12 g) in methanol (100 mL) was stirred until the solution was homogeneous. Sodium iodide (3.98 g) and compound 7a (5.00 g) were added and stirring continued for 30 min. The resulting suspension was cooled to 0 °C and a 5.25% (w/v) aqueous solution of sodium hypochlorite was added dropwise and stirring continued for 1 h. Saturated sodium thiosulfate (25 mL) was added and after 5 min the solution was acidified to pH 2 by addition of 6 N HCl resulting in the formation of a yellow precipitate which was filtered and washed with water (50 mL). The precipitate was transferred to a round-bottomed flask, dissolved in methanol (70 mL) and toluene (100 mL), concentrated, redissolved in methanol (70 mL), concentrated, redissolved again in methanol (70 mL) and toluene (100
- 20
- 25

mL) and concentrated to afford the product as a yellow solid (6.26 g). MS m/z 313 (M-1). ¹H NMR (DMSO-d₆): δ 12.41 (broad, 1 H), 8.63 (s, 1 H), 8.05-7.97 (m, 2 H), 7.70 (m, 1 H), 7.42 (m, 1 H).

7c

5 A solution of compound 7b (8.0 g), dimethyl sulfate (8.03 g), powdered potassium carbonate (8.80 g), and dry acetone (150 mL) was heated under reflux for 18 h. The solution was cooled to room temperature, triethylamine (15 mL) was added, and stirring continued for 30 min. The solution was filtered through a pad of Celite and washed with dry acetone (50 mL). The filtrate was concentrated to a yellow oil, diluted with EtOAc, and washed
10 successively with 1N HCl (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL). The organic phase was dried (sodium sulfate), filtered, concentrated, and purified by chromatography (0-10% EtOAc in hexanes) to afford the product as a yellow oil (5.53 g). ¹H NMR (DMSO-d₆) δ 8.47 (s, 1 H), 8.09 (m, 2 H), 7.74 (m, 1 H), 7.61 (m, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H).

7d

Based on the procedure of Wood, JL; Khatri, NA; Weinreb, SM; Tetrahedron Lett; 51, 4907 (1979), compound c (5.0 g) was suspended in xylenes (100 mL), cooled to 0 °C, dimethylaluminum amide solution (approximately 37 mmol) was added and the solution heated under reflux for 2.5 h. The solution was then cooled to 0 °C, acidified to pH 2 by
20 addition of 1N HCl, and extracted with EtOAc (3x100 mL). The combined EtOAc extracts were washed with saturated aqueous sodium bicarbonate (150 mL) and brine (150 mL), dried (sodium sulfate), filtered, concentrated, and purified by chromatography (1:1 EtOAc:DCM, then 10-20% EtOAc in DCM) to afford the product as a white solid (3.29 g). ¹H NMR (DMSO-d₆): δ 8.69 (s, 1 H), 8.24-8.04 (m, 2 H), 7.91-7.81 (m, 1 H), 7.76-7.65 (m, 1 H), 3.99
25 (s, 3 H); MS m/z 311 (M+1).

7e

Through a suspension of compound 7d (0.250 g), Pd(OAc)₂ (0.018 g), triethylamine (0.081 g) and methanol (20 mL) was bubbled carbon monoxide for 25 min, then stirred at 70 °C under carbon monoxide (1 atm) for 18 h. The cooled solution was filtered, rinsed with
30 methanol (20 mL) and DCM (20 mL), concentrated, preadsorbed onto silica (1 g) and purified by chromatography (0-10% EtOAc in hexanes) to afford the product as a white solid (0.113g). ¹H NMR (DMSO-d₆): δ 8.78 (s, 1 H), 8.12-8.09 (m, 1 H), 7.84-7.78 (m, 2 H), 7.70-7.63 (m, 1 H), 4.02-4.01 (m, 6 H); IR (cm⁻¹): 2228, 1724, 1296, 1236, 1208, 1017.

7f

A flame dried 250 mL 3-neck flask was charged with magnesium metal (2.42 g, 99.5 mmol). After cooling to room temperature, diethyl ether (80 mL), benzene (30 mL) and iodine (12.62 g, 49.7 mmol) were added. The reaction mixture was heated under reflux for 2 h and the iodine color dissipated. After cooling to room temperature, this solution was transferred to compound **7e** (10 g, 41.4 mmol) in benzene (30 mL) via syringe. The flask was washed with benzene (15 mL) and a yellow precipitate formed during the addition. The reaction mixture was heated under reflux for another 1 h. 1N HCl and EtOAc were added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated Na₂S₂O₄, NaCl, water, dried over MgSO₄, filtered and concentrated. The crude product was purified by chromatography (DCM) to afford the product (6.88 g, 73% yield) as a yellow solid. ¹H NMR (CDCl₃) δ 12.82 (s, 1H), 8.81-8.78 (d, 1H), 8.32 (s, 1H), 7.83-7.82 (d, 1H), 7.70 (t, 1H), 7.50 (t, 1H), 4.16 (s, 3H). MS (APCI, negative ion mode) m/z 225.92 (M⁻).

7g

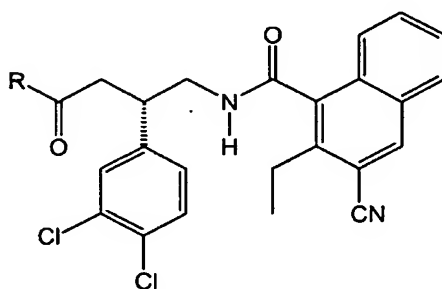
To a solution of compound **7f** (6.24 g, 27.5 mmol) in DCM (140 mL) was added triethylamine (4.21 mL, 30.2 mmol) followed by trifluoromethanesulfonic anhydride (5.05 mL, 30.2 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. Saturated NaHCO₃ was added and the aqueous layer was extracted with DCM. The combined organic extracts were dried over MgSO₄, filtered and concentrated. The crude product was purified by chromatography (eluting with DCM) to give the product (9.6 g, 97% yield) as a yellow oil. ¹H NMR (CDCl₃) δ 8.44 (s, 1H), 8.29-8.04 (d, 1H), 7.01-7.98 (d, 1H), 7.84 (m, 2H), 4.10 (s, 3H).

7h

A stirred solution of compound **7g** (1.51 g, 4.20 mmol), K₃PO₄ (1.78 g, 8.38 mmol), triethylborane (8.4 mL, 8.38 mmol) and (1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium (II) CH₂Cl₂ (0.34 g, 0.42 mmol) in THF (50 mL) was heated at 66 °C for 3 h. Water was added and the mixture was extracted with EtOAc (3x). The combined organic layers were dried over MgSO₄, filter and concentrated. The crude product was purified by chromatography (eluting with 5%, 8% EtOAc/hexane) to give the product (0.66 g, 66% yield) as a yellow oil. MS m/z 240 (M⁺).

7i

To a solution of compound **7h** (0.34 g, 1.42 mmol) in THF (14 mL) and water (5.6 mL) was added 1N NaOH (2.9 mL, 2.98 mmol) and several drops of methanol. The solution was heated under reflux overnight, cooled, THF and methanol were removed under reduced pressure, the mixture was diluted with DCM, then extracted. The aqueous layer was acidified to pH 1 by addition of 1N HCl and extracted with EtOAc. The EtOAc extracts were combined, dried, filtered, and concentrated to afford the product (0.14 g, 44%) as a white solid. MS m/z = 224.

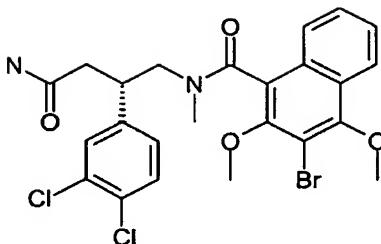


Ex.	R	MS ^a	HPLC ^b	Synthesis ^c
8	-N(CH ₃) ₂	482.1	19.8	N,N-Dimethyl amine
9	-NHCH ₃	468.1	18.3	Methylamine
10	-N(CH ₂ -CH ₂) ₂ O	524.1	19.4	Morpholine

10

^a Mass spectral data; (APCI) m/z . Multiple peaks due to isotopic splitting are not considered; data for the major isotopically abundant signal corresponding to the protonated molecular ion cluster are shown (unless noted otherwise). ^b Analytical HPLC conditions employed were the following: Hewlett Packard HP1050 system using a Zorbax RX-C8, 4.6x250 mm, 5 micron column at 30 °C, with the following gradient: 0-0.5 min; 10% Solvent B, then ramping linearly to 100% Solvent B at 30 min at a fixed flow rate of 1.2 mL/min (Solvent A: 0.1% TFA in water; Solvent B: 0.1% TFA in acetonitrile); UV detection at 215 nm. ^c The compound was prepared by reaction of N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-3-cyano-2-ethyl-1-naphthamide, the indicated amine, and 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride.

20

Example 11

N-[(S)-2-(3,4-Dichlorophenyl)-3-carbamoylpropyl]-N-methyl-3-bromo-2,4-dimethoxy-1-naphthamide

To a stirred solution of N-[2-(3,4-dichlorophenyl)-3-carboxypropyl]-N-methyl-3-bromo-2,4-dimethoxy-1-naphthamide (0.26 g, 0.468 mmol) in 5 mL of DMF was added HOBT•NH₃ (0.175 g, 1.15 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.184 g, 0.96 mmol). The mixture was stirred at RT for 24 h and treated with saturated NaHCO₃. The aqueous layer was extracted with DCM. The combined DCM extracts were dried over MgSO₄, filtered and concentrated. Following chromatography purification, the title compound was obtained as light yellow solid (0.21 g, 81% yield). ¹H NMR (CDCl₃) δ 8.15-8.02 (m), 7.61-7.43 (m), 7.37-7.26 (m), 7.07-7.00 (m), 6.91-6.89 (d), 6.81 (d), 6.70-6.67 (d), 6.56-6.53 (d), 6.14 (s), 5.88 (s), 5.33-5.30 (m), 4.33-4.26 (m), 4.05-3.64 (m), 3.43 (m), 3.25 (s), 3.20 (s), 2.96 (s), 2.89 (s), 2.82-2.55 (m), 1.59 (s). MS m/z 555.0 (M⁺). Analysis calculated for C₂₄H₂₃BrCl₂N₂O₄, 0.1 H₂O, C 51.84, H 4.21, N 5.04, found C 51.81, H 4.31, N 5.05.

The requisite N-[2-(3,4-dichlorophenyl)-3-carboxypropyl]-N-methyl-3-bromo-2,4-dimethoxy-1-naphthamide was prepared as follows:

N-[2-(3,4-Dichlorophenyl)-4-hydroxybutyl]-N-methyl-3-bromo-2,4-dimethoxy-1-naphthamide. 3-Bromo-3,4-dimethoxy-1-naphthoyl chloride (0.6356 g, 1.93 mmol) in 8 mL of DCM was added to a stirred mixture of N-[2-(3,4-dichlorophenyl)-4-hydroxybutyl]amine (0.4785 g, 1.93 mmol) in 24 mL of DCM and 2.4 mL of 1N NaOH at 0 °C. The mixture was stirred at 0 °C for 2 h and RT for 30 min. The aqueous layer was extracted with DCM and the combined DCM extracts were dried over MgSO₄, filtered and concentrated to give crude product which was purified by chromatography to give product as white solid (0.48 g 46% yield). ¹H NMR (CDCl₃) δ 8.11-8.08 (d), 8.06-8.03 (d), 7.63-7.24 (m), 7.14-7.11 (d), 7.03 (d), 6.98-6.88 (m), 6.77-6.74 (d), 6.67-6.64 (d), 6.59-6.56 (d), 4.33-4.25 (m), 4.04-3.81 (m),

3.76 (s), 3.72-3.71 (d), 3.54-3.32 (m), 3.14 (s), 3.10 (s), 2.64 (s), 2.59 (s), 2.11-1.62 (m). MS m/z 542.0 (M⁺).

N-[2-(3,4-Dichlorophenyl)-4-carboxypropyl]-N-methyl-3-bromo-2,4-dimethoxy-1-naphthamide

- 5 To a stirred solution of 0.5 mL of Jones's Reagent (2.734 g of CrO₃ in 2.3 mL of concentrated H₂SO₄ and 10 mL of H₂O) in 5 mL of acetone was added N-[2-(3,4-dichlorophenyl)-4-hydroxybutyl]-N-methyl-3-bromo-2,4-dimethoxy-1-naphthamide (0.35 g, 0.65 mmol) in 5 mL of acetone dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. Isopropyl alcohol was then added until a blue color persisted. The mixture was stirred at RT
- 10 for 15 min and treated with EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organics was washed with saturated NaCl, dried over MgSO₄, filtered and concentrated. Following chromatography purification, the product was obtained as yellow solid (0.26g, 72% yield). ¹H NMR (DMSO-d₆) δ 12.06 (s), 8.08-7.97 (m), 7.76 (s), 7.69-7.48 (m), 7.31-7.21 (m), 7.10-7.08 (d), 6.98-6.95 (d), 6.88-6.83 (t), 6.39-6.36 (d), 4.49-4.41 (t),
- 15 3.97-3.93 (m), 3.81 (s), 3.78 (s), 3.70-3.66 (m), 3.57 (s), 3.48-3.42 (m), 3.10 (s), 3.06 (s), 2.81-2.64 (m), 2.60 (s), 1.85 (s).

The requisite 3-bromo-2,4-dimethoxy-1-naphthoyl chloride for step (a) above was prepared as follows:

Ethyl-3-bromo-2,4-dihydroxy-1-naphthoate

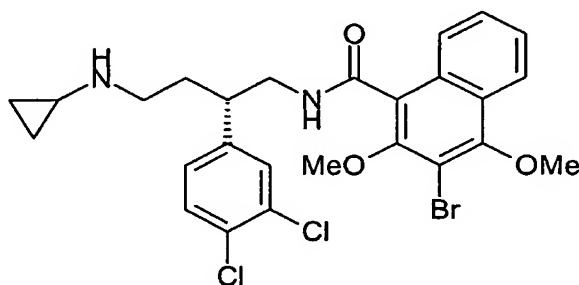
- 20 To a solution of ethyl-2,4-dihydroxy-1-naphthoate [Bruggink and McKillop Tetrahedron 31, 2607, 1975] (0.1 g, 0.43 mmol) in acetonitrile (2 mL) was added NBS (84 mg, 0.47 mmol). The mixture was stirred at RT for 30 min. The acetonitrile was removed in vacuo and CCl₄ was added. The solution was filtered and concentrated. The crude product was purified by chromatography (eluting with DCM) to give the product (0.13 g, 93% yield)
- 25 as a white solid. ¹H NMR (CDCl₃) δ 13.61 (s, 1H), 8.79 (d, 1H), 8.24 (d, 1H), 7.58 (t, 1H), 7.41 (t, 1H), 6.61 (s, 1H), 4.60 (q, 2H), 1.55 (t, 3H). MS APCI negative mode m/z 310.84.
- Ethyl-3-bromo-2,4-dimethoxy-1-naphthoate

- To a solution of ethyl-3-bromo-2,4-dihydroxy-1-naphthoate (5.8 g, 18.6 mmol) in acetone (93 mL) was added potassium carbonate (6.43 g, 46.6 mmol) and dimethyl sulfate
- 30 (4.4 mL, 46.6 mmol). The mixture was heated under reflux overnight and solvent was removed in vacuo. Water and EtOAc was added and the organic layer was dried over MgSO₄, filtered and concentrated. The crude product was purified by chromatography (eluting with 3-5% EtOAc/hexane) to give the product (6.23 g, 99% yield) as a light yellow

oil. ^1H NMR (CDCl_3) δ 8.13 (d, 1H), 7.83 (d, 1H), 7.62-7.48 (m, 2H), 4.54 (q, 2H), 4.02 (s, 3H), 4.00 (s, 3H), 1.46 (t, 3H).

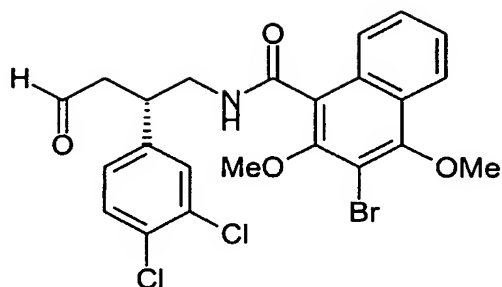
3-Bromo-2,4-dimethoxy-1-naphthoyl chloride

A solution of ethyl-3-bromo-2,4-dimethoxy-1-naphthoate (0.613 g) in THF (6 mL) and water (4 mL) was treated with $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.16 g). Methanol (0.5 mL) was added, and the mixture was stirred under reflux for 40 h. The mixture was concentrated, treated with additional H_2O and extracted with DCM. The aqueous layer was acidified with 1N HCl and extracted with EtOAc. The extracts were dried, filtered, and the solvent removed to afford the product (0.33 g, 59% yield) as a white solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.73 (s, 1H), 8.09 (d, 1H), 7.82 (d, 1H), 7.71-7.56 (m, 2H), 3.97 (s, 3H), 3.91 (s, 3H). This material was converted to 3-bromo-2,4-dimethoxy-1-naphthoyl chloride using oxalyl chloride under standard conditions.

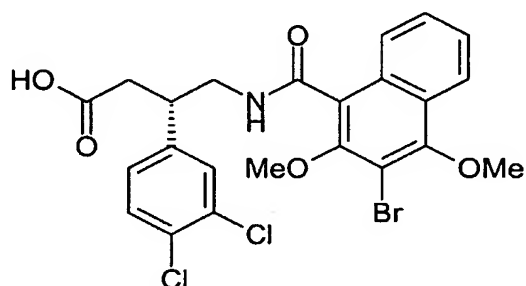


Example 12

Example 12 was synthesized by standard reductive amination with cyclopropylamine and aldehyde. The required aldehyde was prepared as follows:
N-[2-(S)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-3-bromo-2,4-dimethoxy-1-naphthamide
A solution of N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]amine in DCM was combined with 1N NaOH solution. The mixture was cooled to 0 °C and a solution of 3-bromo-2,4-dimethoxy-1-naphthoyl chloride in DCM was added dropwise over 30 min. After stirring overnight at room temperature, the organic phase was concentrated and purified by column chromatography to afford N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-3-bromo-2,4-dimethoxy-1-naphthamide. ^1H NMR (300 MHz, CDCl_3) δ 8.07-8.03 (m, 1H), 7.68-7.62 (m, 1H), 7.51-7.38 (m, 4H), 7.16-7.13 (dd, 1H), 6.08 (t, 1H), 3.99 (s, 3H), 3.87 (s, 3H), 3.87-3.70 (m, 3H), 3.56 (m, 1H), 3.23-3.15 (m, 1H), 2.13-2.02 (m, 1H), 1.92-1.81 (m, 1H); MS APCI, m/z = 528 (M^+).



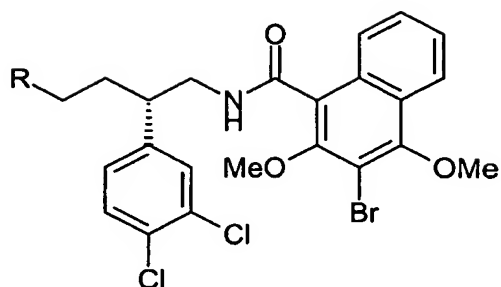
The aldehyde was prepared by standard Swern oxidation of N-[2-(S)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-3-bromo-2,4-dimethoxy-1-naphthamide. MS APCI, $m/z = 526$ (M^+).



5 **Example 13**

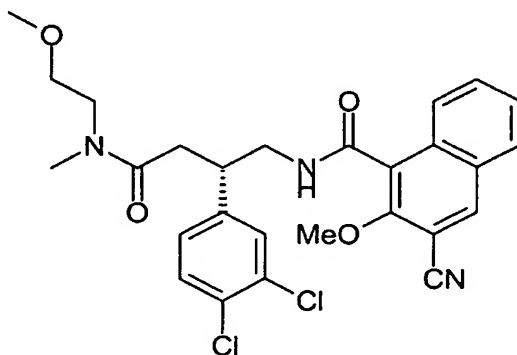
N-[2-(S)-(3,4-Dichlorophenyl)-3-carboxypropyl]-3-bromo-2,4-dimethoxy-1-naphthamide

- To a solution of Jones's Reagent (prepare from 2.734g of CrO_3 , 2.3 mL of concentrated H_2SO_4 and 10 mL of water) (2.4 mL) in acetone (20 mL) was added a solution of N-[2-(S)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-3-bromo-2,4-dimethoxy-1-naphthamide (1.647 g, 3.12 mmol) in acetone (20 mL) dropwise at 0°C . The mixture was stirred at 0°C for 2 h. Isopropyl alcohol was added until a blue color was persisted. The mixture was stirred 15 min at room temperature and EtOAc/water was added. Combined organic layer was washed with saturated NaCl, dried over MgSO_4 , filtered and concentrated, following chromatography purification to give product as a white solid (1.07 g, 63% yield). ^1H NMR (CDCl_3) δ 8.08-8.04 (m, 1H), 7.68-7.64 (m, 1H), 7.52-7.46 (m, 2H), 7.42-7.40 (m, 2H), 7.18-7.15 (dd, 1H), 6.09 (t, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 3.88-3.75 (m, 2H), 3.53-3.44 (m, 1H), 2.95-2.70 (m, 2H). MS (APCI) m/z 542.18 ($M+1$).



Ex.	R	MS	HPLC	Synthesis
12		567	3.629	Cyclopropylamine (1.5 equiv.)
14	-NMe ₂	555	3.493	Dimethylamine HCl (1.5 equiv.)
15	-NEt ₂	583	3.675	Diethylamine (1.5 equiv.)
16	-NMe(CH ₂) ₂ -OH	585	3.413	2-(methylamino)ethanol (1.5 equiv.)

- 5 Analytical HPLC conditions employed were the following: Hewlett Packard HP1100 system using a Luna C₁₈(2) 4.6x75 mm, 3 micron column with the following gradient: 20% -90% Solvent B 6 min at a fixed flow rate of 2 mL/min (Solvent A: 0.1% TFA in water; Solvent B: 0.1% TFA in acetonitrile) using UV detection at 255 nm



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Example 17

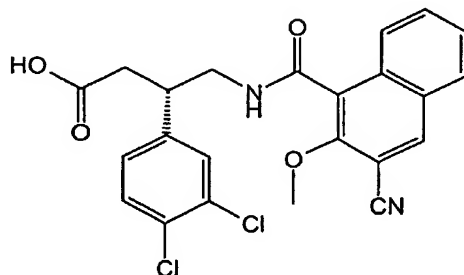
The solution of N-[2-(S)-(3,4-Dichlorophenyl)-3-carboxypropyl]-3-cyano-2-methoxy-1-naphthamide (0.15 g, 0.33 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (0.144 g, 0.75 mmol), 1-hydroxybenzotriazole (0.11 g, 0.81 mmol) and N-(2-methoxyethyl)methylamine (0.108 g, 1.22 mmol) in DMF (2 mL) was stirred at room temperature for 5 min. Triethylamine (0.22 mL, 1.62 mmol) was added and the solution was stirred at room temperature over night. EtOAc and saturated NaHCO₃ was added. The organic layer was dried over MgSO₄, filtered and concentrated. After chromatography purification, the product was obtained as light yellow solid (0.132 g, 76% yield).

The required acid was prepared as follows:

N-[2-(S)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-3-cyano-2-methoxy-1-naphthamide

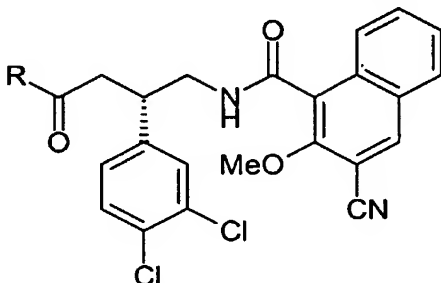
A solution of N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]amine in DCM was combined with 1N NaOH solution. The mixture was cooled to 0 °C and a solution of 3-cyano-2-methoxy-1-naphthoyl chloride in DCM was added dropwise over 30 min. After stirring overnight at room temperature, the organic phase was concentrated and purified by column chromatography to afford N-[2-(S)-(3,4-dichlorophenyl)-4-hydroxybutyl]-3-cyano-2-methoxy-1-naphthamide. ¹H NMR (300 MHz, CDCl₃) δ 8.19 (s, 1H), 7.83-7.80 (d, 1H), 7.66-7.50 (m, 3H), 7.43-7.38 (m, 2H), 7.17-7.14 (dd, 1H), 6.10 (t, 1H), 4.01 (s, 3H), 3.92-3.68 (m, 3H), 3.60-3.52 (m, 1H), 3.23-3.17 (m, 1H), 2.13-2.02 (m, 1H), 1.93-1.82 (m, 1H); MS APCI, m/z = 443 (M⁺).

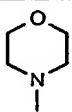
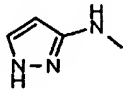
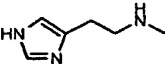
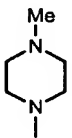
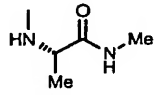


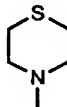
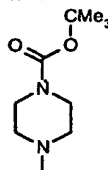
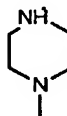
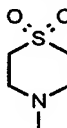
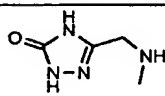
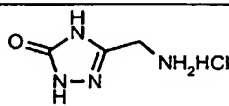
N-[2-(S)-(3,4-Dichlorophenyl)-3-carboxypropyl]-3-cyano-2-methoxy-1-naphthamide

To a solution of Jones Reagent (prepare from 2.734 g of CrO₃, 2.3 mL of concentrated H₂SO₄ and 10 mL of water) (13 mL) in acetone (100 mL) was added a solution of N-[2-(S)-(3,4-Dichlorophenyl)-4-hydroxybutyl]-3-cyano-2-methoxy-1-naphthamide (7.53g, 17 mmol) in acetone (100 mL) dropwise at 0°C. The mixture was stirred at 0 °C for 2 h. Isopropyl alcohol was added until a blue color was persisted. The mixture was stirred 15 min at room temperature and EtOAc/water was added. Combined organic layer was washed with saturated NaCl, dried over MgSO₄, filtered and concentrated, following chromatography purification to give product as a yellow solid (6.99g, 90%yield). ¹H NMR (CDCl₃) δ 8.19 (s,

1H), 7.84-7.81 (d, 1H), 7.65-7.41 (m, 5H), 7.19-7.15 (dd, 1H), 6.15 (t, 1H), 4.00 (t, 3H), 3.93-3.76 (m, 2H), 3.54-3.45 (m, 1H), 2.94-2.70 (m, 2H). MS (APCI) m/z 479.2 (M+Na).



Ex.	R	MS	HPLC	Synthesis
17	-N(Me)CH ₂ -CH ₂ OMe	528	14.78 ^a	N-(2-methoxyethyl)methylamine (3.7 equiv)
18	-NHC(Me) ₂ -CH ₂ OH	528	14.01 ^a	2-amino-2-methyl-1-propanol (3.7 equiv.)
19		527	14.24 ^a	Morpholine (3.7 equiv.)
20		522	17.80 ^a	3-aminopyrazole (3.7 equiv.)
21		550	2.06 ^b	Histamine (3.7 equiv.)
22		539	3.08 ^c	N-methylpiperazine (3.7 equiv.)
23	-N(Me)CH ₂ -CONH ₂	527	3.41 ^c	N-Me-Gly-NH ₂ HCl (3.7 equiv.)
24		563	3.51 ^c	H-Ala-NH-Me HCl (3.7 equiv.)

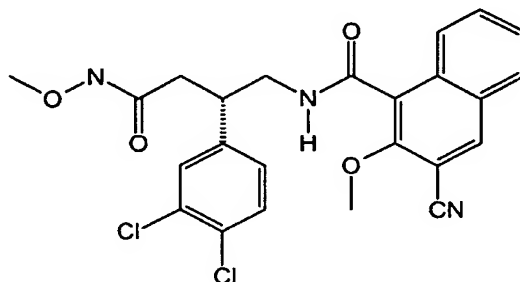
Ex.	R	MS	HPLC	Synthesis
25		542	4.44°	Thiomorpholine (3.7 equiv.)
26		647	4.77°	tert-butyl-1-piperazinecarboxylate (3.7 equiv.)
27		525	3.00°	TFA (20 equiv.) from example 26
28	-NH(Me)- CH ₂ CONMe ₂	555	3.80°	N-methyl-Gly-N(Me) ₂ (3.7 equiv.)
29		574	3.94°	KHSO ₅ (49.5% in water) (1.5 equiv.) from example 25
30	-N(Et)CONH. (CH ₂) ₃ NMe ₂	612	3.42°	Benzenesulfonamide (3.7 equiv.)
31	-NHNMe ₂	499	2.11 ^b	1,1-dimethylhydrozine (3.7 equiv.)
32		553	1.98 ^b	
33	-N(Me)CH ₂ - CH ₂ OH	514	3.66°	MeNHCH ₂ CH ₂ OTBDMSi (3.7 equiv.) followed by TBAF (2.4 equiv.)

Analytical HPLC conditions employed were the following:

- ^a Analytical HPLC conditions employed were the following: Hewlett Packard HP1100 system using a C8 2.5x250 nm column with the gradient 10% -100% Solvent B in 20 min at a flow rate of 1.2 mL/min (Solvent A: 0.1% TFA in water; Solvent B: 0.1% TFA in acetonitrile) using UV detection at 255 nm.

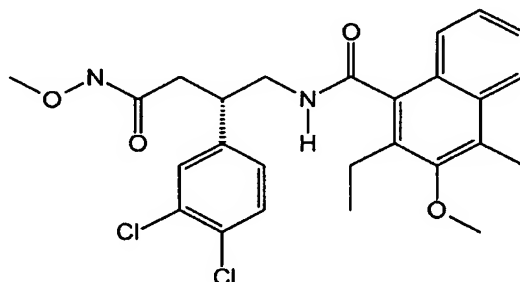
^b Analytical HPLC conditions employed were the following: LCMS system using a Zorbax C8 2.2x50 mm column with the gradient: 5% -90% Solvent B in 3 min at a flow rate of 1.4 mL/min (Solvent A: 0.05% TFA in water; Solvent B: 90% acetonitrile 10% water 0.05% TFA) using UV detection at 215 nm.

- 5 ^c Hewlett Packard HP1100 system using a Luna C18(2) 4.6x75 mm, 3 micron column with the gradient: 20% -90% Solvent B in 6 min at a flow rate of 2 mL/min (Solvent A: 0.1% TFA in water; Solvent B: 0.1% TFA in acetonitrile) using UV detection at 255 nm.



Example 34

- 10 Example 34 was prepared by reaction of N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-3-cyano-2-methoxy-1-naphthamide with methoxylamine according to the procedure described for Example 3. ¹H NMR (300 MHz, CDCl₃) δ 9.10 (s, 1H), 8.18 (s, 1H), 7.82 (d, 1H), 7.61-7.16 (m, 6H), 6.32 (m, 1H), 4.02 (m, 4H), 3.69 (m, 4H), 3.48 (m, 1H), 2.85-2.45 (m, 2H).; MS APCI, m/z = 486 (M⁺). Analysis calculated for C₂₄H₂₁N₃O₄Cl₂ 0.5 H₂O·C
- 15 58.19, H 4.47, N 8.48, found C 58.11, H 3.97, N 8.32.



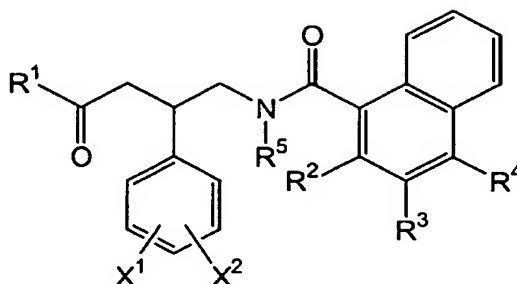
Example 35

- Example was prepared by reaction of N-[2-(S)-(3,4-dichlorophenyl)-3-carboxypropyl]-2-ethyl-3-methoxy-4-methyl-1-naphthamide with methoxylamine according to the procedure described for Example 3. ¹H NMR (300 MHz, CDCl₃) δ 9.43 (s, 1H), 7.89 (d, 1H), 7.46-7.36 (m, 5H), 7.11 (m, 1H), 5.98 (m, 1H), 4.05 (m, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.68-3.44 (m, 3H), 2.65-2.40 (m, 3H), 2.56 (s, 3H), 1.18 (m, 3H).; MS APCI, m/z = 503 (M⁺). Analysis
- 20

calculated for $C_{26}H_{28}N_2O_4Cl_2 \cdot 0.6 H_2O$ C 55.08, H 5.74, N 4.01, found C 55.09, H 5.78, N 3.88.

CLAIMS:

1. A compound having the formula



- 5 wherein:

R¹ is -OR⁶, -NR⁶R⁷, -NOC₁₋₆alkyl or -NR⁷NR⁶R⁷;

R^2 is $-OR^6$ or C_{1-12} alkyl;

R^3 is H, halogen, $-OR^7$ or $-CN$;

R^4 is H, C_{1-6} alkyl or $-OR^7$;

- 10 R^5 is H or C_{1-6} alkyl;

R⁶ is independently, at each instance, H, C₁₋₆alkyl, R⁷OC₁₋₆alkyl-, R⁷OC(=O)C₁₋₆alkyl-,

R^6 is independently, at each instance, H, $C_{1-6}alkyl$, $R^7OC_{1-6}alkyl$ -, $R^7OC(=O)C_{1-6}alkyl$ -, $R^7R^7NC(=O)C_{1-6}alkyl$ -, $R^7R^7NC_{1-6}alkylNR^7C(=O)$ -, R^8 -, $R^8C_{1-6}alkyl$ - or $-(CH_2)_mphenyl$, wherein the phenyl is substituted by 1, 2 or three substituents selected from $C_{1-6}alkylthio$, $C_{1-6}alkylsulfinyl$, $C_{1-6}alkylsulfonyl$, trifluoromethylthio, trifluoromethylsulfinyl,

- 15 C₁₋₆alkanesulfonamido, C₁₋₆alkanoyl, C₁₋₆alkoxy-carbonyl, succinamido, carbamoyl, C₁₋₆alkylcarbamoyl, di-C₁₋₆alkylcarbamoyl, C₁₋₆alkoxy-C₁₋₆alkylcarbamoyl, N-methylcarbamoyl, C₁₋₆alkanoylamino, ureido, C₁₋₆ureido, di-C₁₋₆alkylureido, amino, C₁₋₆alkylamino and di-C₁₋₆alkylamino;

R⁷ is independently, at each instance, H or C₁₋₆alkyl; or

- 20 R⁶ and R⁷ together are -(CH₂)₂O(CH₂)₂-, -(CH₂)₂S(=O)_m(CH₂)₂-,
-(CH₂)₂N(CO₂R⁷)(CH₂)₂- or -(CH₂)₂NR⁷(CH₂)₂-;

R⁸ is a 5- or 6-membered saturated or unsaturated heterocycle containing 1, 2 or 3 nitrogen atoms and additionally substituted with 0 or 1 oxo groups;

m is independently, at each instance 0, 1 or 2; and

- 25 X¹ and X² are independently H, -CH₃, or halogen; or
any pharmaceutically-acceptable salt thereof.

2. A compound according to Claim 1 wherein X¹ and X² are H or halogen, and at least one of X¹ and X² are halogen.

one of X^1 and X^2 are halogen.

3. A compound according to Claim 1, wherein R^1 is $-OR^6$.
4. A compound according to Claim 1, wherein R^1 is $-NR^6R^7$.
5. A compound according to Claim 1, wherein:
 - R^2 is $-\text{CH}_2\text{CH}_3$ or $-\text{OCH}_3$,
 - 5 R^3 is $-\text{CN}$; and
 - R^5 is H.
6. A compound according to Claim 1, wherein:
 - R^1 is $-OR^6$ or $-NR^6R^7$;
 - R^2 is $-OR^6$ or $\text{C}_{1-12}\text{alkyl}$;
 - 10 R^3 is H, halogen or $-\text{CN}$;
 - R^4 is H, $\text{C}_{1-6}\text{alkyl}$ or $-OR^7$;
 - R^5 is H or $\text{C}_{1-6}\text{alkyl}$;
 - R^6 is independently, at each instance, H, $\text{C}_{1-6}\text{alkyl}$ or $-(\text{CH}_2)_m\text{phenyl}$, wherein the phenyl is substituted by 1, 2 or three substituents selected from $\text{C}_{1-6}\text{alkylthio}$, $\text{C}_{1-6}\text{alkylsulfinyl}$, $\text{C}_{1-6}\text{alkylsulfonyl}$, trifluoromethylthio, trifluoromethylsulfinyl, $\text{C}_{1-6}\text{alkanesulfonamido}$, $\text{C}_{1-6}\text{alkanoyl}$, $\text{C}_{1-6}\text{alkoxy-carbonyl}$, succinamido, carbamoyl, $\text{C}_{1-6}\text{alkylcarbamoyl}$, di- $\text{C}_{1-6}\text{alkylcarbamoyl}$, $\text{C}_{1-6}\text{alkoxy-C}_{1-6}\text{alkylcarbamoyl}$, N-methylcarbamoyl, $\text{C}_{1-6}\text{alkanoylamino}$, ureido, $\text{C}_{1-6}\text{ureido}$, di- $\text{C}_{1-6}\text{alkylureido}$, amino, $\text{C}_{1-6}\text{alkylamino}$ and di- $\text{C}_{1-6}\text{alkylamino}$;
 - 15 R^7 is H or $\text{C}_{1-6}\text{alkyl}$;
 - m is 0, 1 or 2; and
 - X^1 and X^2 are independently H, $-\text{CH}_3$ or halogen; or any pharmaceutically-acceptable salt thereof.
7. A compound according to Claim 6 wherein X^1 and X^2 are H or halogen, and at least
 - 25 one of X^1 and X^2 are halogen.
8. A compound according to Claim 7, wherein R^1 is $-OR^6$.
9. A compound according to Claim 7, wherein R^1 is $-NR^6R^7$.
10. A compound according to Claim 7, wherein R^3 is $-\text{CN}$.
11. A compound according to Claim 7, wherein R^5 is H.
- 30 12. A compound according to Claim 7, wherein R^2 is $-\text{CH}_2\text{CH}_3$ or $-\text{OCH}_3$.
13. A pharmaceutical composition comprising a compound according to any one of Claims 1 through 12.

14. A method of treating major depressive disorder, severe anxiety disorders, stress disorders, major depressive disorder with anxiety, eating disorders, bipolar disorder, general or specific craving, substance use disorder, schizophrenic disorders, psychotic disorders, movement disorders, cognitive disorders, depression and/or anxiety, mania or hypomania, aggressive behaviour, obesity, emesis, rheumatoid arthritis, Alzheimer's disease, cancer, oedema, allergic rhinitis, inflammation, pain, gastrointestinal-hypermotility, Huntington's disease, COPD, hypertension, migraine, bladder hypermotility, or urticaria comprising administering an effective amount of an NK1 antagonist according to any one of Claims 1 through 7.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00752

A. CLASSIFICATION OF SUBJECT MATTER C07C 233/66, 235/66;
 C07D 233/64, 233/88, 241/04, 249/12, 265/30, 279/12, 285/15; A61K 31/166, 192, 277, 415,
 IPC7: 4164, 4196, 495, 5375, 54; A61P 3/04 9/12, 13/00, 23/00, 25/00, 29/00, 35/00, 37/00
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS DATA, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0002859 A1 (ZENECA LIMITED), 20 January 2000 (20.01.00), abstract; page 2, line 21 - page 3, line 7; page 105, lines 14-16 --	14
X	Clin. Exp. Allergy, Volume 29, No 2, 1999, Schuiling, M. et al, "Role of tachykinin NK1 and NK2 receptors in allergen-induced early and late asthmatic reactions, airway hyperresponsiveness, and airway inflammation in conscious, unrestrained guinea pigs", page 48 - page 52, (The compounds SR 48968 and SR 140333 taken together.) --	14

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2001	17 -08- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00752

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Eur. J. Pharmacol., Volume 361, No 2/3, 1998, Coudore-Civiale, Marie-Ange et al, "Effect of tachykinin receptor antagonists in experimental neuropathic pain", page 175 - page 184, (The compounds SR 48968 and SR 140333 taken together.) --	14
X	Life Sci., Volume 63, No 4, 1998, Mazelin, Ludmilla et al, "Comparative effects of nonpeptide tachykinin receptor antagonists on experimental gut inflammation in rats and guinea-pigs", page 293 - page 304, (The compounds SR 48968 and SR 140333 taken together.) --	14
P,A	WO 0020003 A1 (ZENECA LIMITED), 13 April 2000 (13.04.00) --	1-14
P,A	WO 0020389 A1 (ZENECA LIMITED), 13 April 2000 (13.04.00) --	1-14
P,A	WO 0034243 A1 (ASTRAZENECA UK LIMITED), 15 June 2000 (15.06.00) --	1-14
P,A	WO 0064423 A2 (SANOFI-SYNTHELABO), 2 November 2000 (02.11.00) --	1-14
P,A	Eur. J. Pharmacol., Volume 415, No 1, 2001, Giuliani, S. et al, "Effect of a tachykinin NK2 receptor antagonist, nepadutant, on cardiovascular and gastrointestinal function in rats and dogs", page 61 - page 71, Abstract (states antihypertensive effects of SR 48968) --	14

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/00752

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9628158 A1 (PFIZER LIMITED), 19 Sept 1996 (19.09.96) --	1-14
A	US 5998439 A (GEORGE P. MAYNARD ET AL), 7 December 1999 (07.12.99) --	1-14
A	US 5789422 A (GREGORY A. REICHARD ET AL), 4 August 1998 (04.08.98) -- -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00752

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/00752

Claim 14 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/07/01

International application No.

PCT/SE 01/00752

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	0002859	A1	20/01/00	AU	4637899 A	01/02/00
				BR	9912013 A	10/04/01
				EP	1097137 A	09/05/01
				GB	9814886 D	00/00/00
				GB	9914886 D	00/00/00
				NO	20010151 A	05/03/01
				AU	6111199 A	26/04/00
				GB	9821699 D	00/00/00
				GB	9922521 D	00/00/00
				NO	20011765 D	00/00/00
				WO	0020389 A	13/04/00
				AU	6111099 A	26/04/00
				GB	9821703 D	00/00/00
				GB	9922519 D	00/00/00
				NO	20011766 D	00/00/00
				WO	0020003 A	13/04/00
				GB	9909840 D	00/00/00
WO	0020003	A1	13/04/00	AU	4637899 A	01/02/00
				AU	6111099 A	26/04/00
				BR	9912013 A	10/04/01
				EP	1097137 A	09/05/01
				GB	9821703 D	00/00/00
				GB	9914886 D	00/00/00
				GB	9922519 D	00/00/00
				NO	20010151 A	05/03/01
				NO	20011766 D	00/00/00
				WO	0002859 A	20/01/00
WO	0020389	A1	13/04/00	GB	9905238 D	00/00/00
				AU	4637899 A	01/02/00
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				BR	9912013 A	10/04/01
				EP	1097137 A	09/05/01
				GB	9821699 D	00/00/00
				GB	9914886 D	00/00/00
				GB	9922521 D	00/00/00
				NO	20010151 A	05/03/01
				NO	20011765 D	00/00/00
				WO	0002859 A	20/01/00
				GB	9906278 D	00/00/00
WO	0034243	A1	15/06/00	GB	9909839 D	00/00/00
				AU	1667500 A	26/06/00
WO	0064423	A2	02/11/00	GB	9826941 D	00/00/00
				AU	4303400 A	10/11/00
WO	9628158	A1	19/09/96	FR	2792835 A,B	03/11/00
				GB	9505084 D	00/00/00

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/07/01

International application No.
PCT/SE 01/00752

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
US	5998439	A	07/12/99	AU 709215 B	26/08/99
				AU 2270797 A	10/09/97
				BR 9707643 A	27/07/99
				CA 2246727 A	28/08/97
				CN 1211247 A	17/03/99
				EP 0882038 A	09/12/98
				HU 9901751 A	30/08/99
				IL 125577 D	00/00/00
				NO 983831 A	20/10/98
				WO 9730990 A	28/08/97

US	5789422	A	04/08/98	NONE	
